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REVIEW

Cardiac wasting in patients with advanced cancer: state of the art review

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Abstract

Cardiac wasting, a complex and understudied phenomenon, is observed in up to 40% of patients with advanced cancer, contributing to 20-30% of mortality within this cohort. This condition represents a significant determinant of impaired quality of life and increased mortality, highlighting its clinical importance. Numerous pathophysiological mechanisms have been identified in clinical and pre-clinical research as key drivers in the development and progression of cardiac wasting, including elevated circulating inflammatory cytokines, enhanced catabolic processes, hormonal dysregulation, dysfunction of the growth hormone-insulin-like growth factor I (GH-IGF-I) axis, oxidative stress, psychosocial factors, myosin heavy chain isoform switching, and, critically, cardiotoxic effects of anticancer therapies. Clinically, cardiac wasting manifests through a spectrum of symptoms and consequences, including muscle wasting, heart failure-like symptoms, impaired global longitudinal strain (GLS), and structural and functional alterations in the heart, particularly within the left ventricle. These cardiac alterations contribute to progressive cardiovascular decline. Preclinical and clinical studies have confirmed these observations across various models and patient cohorts, demonstrating significant cardiac changes, such as a 33% reduction in cardiomyocyte cross-sectional area, up to 21% decrease in left ventricular mass and 11% reduction in heart weight, and a 50% reduction in left ventricular axon length. Additionally, fibrosis in pre-clinical studies, preservation of left ventricular ejection fraction in some studies, and mild decreases in others, along with an 8.1% reduction in GLS and a 12.1% loss in left ventricular wall thickness, are observed, in conjunction with elevated circulating levels of interleukin-6 (IL-6). Given the substantial morbidity and mortality associated with cardiac wasting in advanced cancer, it is imperative to incorporate comprehensive cardiac assessment into routine follow-up care, refine patient stratification strategies, employ advanced diagnostic technologies in clinical trials, and prioritize research into the cardiovascular impacts of cancer treatments. A concerted focus on advancing the field of cardio-oncology is essential for mitigating the adverse outcomes of cardiac wasting in this vulnerable patient population.

Key words: populations; cardio-oncology.

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Introduction

Cardiac wasting, characterized by the progressive loss of heart muscle, is an emerging phenomenon in both cardiology and oncology, with significant implications for patient prognosis.[1,2] This condition could potentially account for 20% to 30% of non-cancer-related mortality in patients with advanced stage cancer disease.[3] Between 30% and 80% of these patients develop cachexia, a syndrome marked by more than 5% weight loss over past 6 months, Body mass index (BMI) less than 20 and any degree of weight loss above 2% or appendicular skeletal muscle wasting and any degree of weight loss above 2%, according to a diagnostic panel.[4,5]

The connection between cancer and cardiac wasting is reinforced by a variety of pathophysiological processes, including

systemic inflammation, metabolic and hormonal dysregulation, altered gene expression, hypo- or hyper-active signalling processes, autophagy, oxidative stress, and the psychosocial burden of chronic illness.[6-8] Furthermore, cardiotoxicity induced by certain anticancer therapies, and the psychosocial stress accompanying chronic illnesses are emerging as significant contributing factors to cardiac dysfunction.[9,10]

Symptoms of cardiac wasting often mirror those of heart failure, including exercise intolerance, dyspnoea, and a marked decline in quality of life.[7,11,12] Current cancer-focused palliative care strategies sometimes neglect the distinct cardiovascular components of this syndrome, highlighting the need for more comprehensive management. Thus, it is essential to address the coexistence of cancer, cachexia, and cardiac wasting in these patients, to better understand the underlying mechanisms of dysfunction and, ultimately, mortality.[6]

Structurally, the atrophied heart in cardiac wasting exhibits several key features as shown in pre-clinical models: increased myocardial fibrosis, reduced left ventricular mass, decreased cardiomyocyte cross-sectional area, and significant loss of protein content.[13,14] Functionally, the left ventricular ejection fraction may either decline or remain preserved as a compensatory mechanism; however, global longitudinal strain, which measures the extent of myocardial shortening during systole, is notably diminished in animal models, potentially explaining the symptoms accompanying cardiac wasting.[15-17]

This state-of-the-art review aims to explore the aetiology and consequences of cardiac wasting in advanced stage cancer patients, providing an overview of both preclinical and clinical evidence. It will also discuss the future directions for research and potential clinical implications for improving patient care in this challenging clinical scenario.

Pathophysiology of cardiac wasting in advanced cancer patients

Cardiac wasting has a significant contribution to early mortality in patients with advanced cancer, yet its pathophysiology remains underexplored in today's healthcare systems. This condition is multifactorial, with key contributors including the direct effects of cancer on cardiac function, the cardiotoxicity of anti-cancer therapies, and the often-overlooked influence of psychosocial stress. This section aims to provide a scientific understanding of the aetiology behind cardiac cachexia in cancer patients and to highlight the areas requiring further research.

Systemic inflammation, a hallmark of cancer, plays a central role in cardiac cachexia, since it involves the release of cytokines such as IL-1, IL-6, and Tumor Necrosis Factor-Alpha (TNF-α), all of which could be cardiotoxic and potentially contribute to mitochondrial dysfunction, metabolic dysregulation, and impaired glucose uptake, accelerated tumour growth, and enhanced cardiac wasting.[8,18-20] These cytokines induce a cascade of intracellular signalling pathways, including activation of nuclear factor kappa B (NF-κB), mitogen-activated protein kinases (MAPKs), and caspases, which promote apoptosis and local inflammation in cardiac tissue. Studies by Tian *et al*. in C26 tumor-bearing mice have confirmed the pivotal role of IL-6 in this process, focusing on its involvement in the activation of these pathways, thereby exacerbating cardiac dysfunction.[21,22]

Cancer cachexia is characterized by metabolic dysfunction, seen as high catabolism and low anabolism, leading to significant muscle wasting, including cardiac atrophy.[23-25] This imbalance is driven by the activation of ubiquitin ligases, and consequently, the ubiquitin-proteasome system, which accelerates the degradation of muscle proteins such as troponin I in cardiac muscle fibers.[18] As a result, there is a marked reduction in cardiac muscle mass, particularly in the left ventricle, which contrasts with the left ventricular hypertrophy observed in patients with chronic heart failure.[19,26,27]

In advanced cancer, hormonal dysregulation is another critical factor affecting cardiac health. Notably, cancer-mediated insulin insufficiency, due to excessive glucose consumption by tumor cells, results in reduced insulin availability and glucose uptake by cardiomyocytes, which ultimately might compromise cardiac energy metabolism and contractility.[8] Moreover, Insulin-like Growth Factor I (IGF-I), which typically counteracts apoptotic signals directed at cardiomyocytes and improves their survival, is often depleted in cancer.[28] The Growth Hormone (GH) has anabolic effects on hepatic IGF-1 synthesis, a key mediator of cellular growth.[29] This process involves multiple receptors and binding proteins, including Growth Hormone Binding Protein (GHBP) and Insulin-like Growth Factor Binding Protein 3 (IGFBP3).[30] A study by Frohlich *et al*. establishes a critical link between cardiac wasting in advanced cancer patients and the acquired GH resistance observed in cachexia.[29] This resistance is characterized by a reduction in GH receptors or binding proteins (e.g., GHBP), coupled with elevated circulating GH levels and decreased IGF-1 concentrations, leading to an impaired GH-IGF-I axis.[29] In multiple studies, these alterations have shown to be positively correlated to the loss of left ventricular mass, a hallmark of cardiac dysfunction in this patient population.[31-33]

A critical molecular mechanism contributing to cardiac dysfunction in advanced cancer patients might be gene switching in myosin heavy chains (MyHC). The MyHC shifts from an adult (alpha) isoform, exhibiting a greater contractile velocity, to a fetal (beta) phenotype, having slower contractions.[34] This predominance of beta-MyHC in the myocardium induces sarcomere destabilization and severe changes in cardiac function.[6,34,35] These effects are observed in failing hearts, due to mitochondrial dysfunction, impaired glucose and fatty acid metabolism and the already worsening condition of the heart.[34,35]

In advanced cancer patients, oxidative stress is a well-established cause of cardiac damage in cancer patients, through the increased production of reactive oxygen species.[9] This production occurs both endogenously due to an increased metabolic rate, genetic mutation, and hypoxic conditions, and exogenously due to cardiotoxic anti-cancer therapeutic agents, the most discussed being anthracyclines (e.g., doxorubicin and idarubicin).[9] Notably, the metabolism of doxorubicin causes the release of

reactive oxygen species (ROS), which leads to myocardial cell death by activating apoptotic mechanisms, such as caspase 3 and 9 and p38 mitogen-activated protein kinases (MAPK).[36-42] Furthermore, these ROS alter cardiolipin, a mitochondrial phospholipid, exacerbating the release of cytochrome C from the mitochondrial matrix to the cytosol and ultimately, amplifying the rate of apoptosis.[43,44] The cumulative effect of this cardiotoxicity is a decline in left ventricular ejection fraction (LVEF), with a dose-dependent relationship.[45]

In addition to the physiological factors contributing to cardiac cachexia, psychosocial stress is an often-overlooked yet potentially significant etiological factor. Merz *et al*. highlighted its role in the exacerbation of cardiovascular disorders, particularly in patients showing recurrent cardiac events despite receiving optimal treatments for traditional risk factors.[10] Because the link between psychosocial stress and cardiac dysfunction in cancer cachexia remains underexplored, more research is needed to directly establish this link and understand its potential impact on the pathophysiology of cardiac wasting. The pathophysiology of cardiac wasting in advanced cancer is summarized in Figure 1.

Clinical and functional consequences of cardiac wasting

In today's healthcare system, clinical manifestations of cardiac wasting are predominantly overlooked, primarily due to the focus on cancer-oriented management and the lack of systematic cardiovascular assessment.[7] However, emerging research literature suggests that cardiac atrophy occurs in up to 40% of

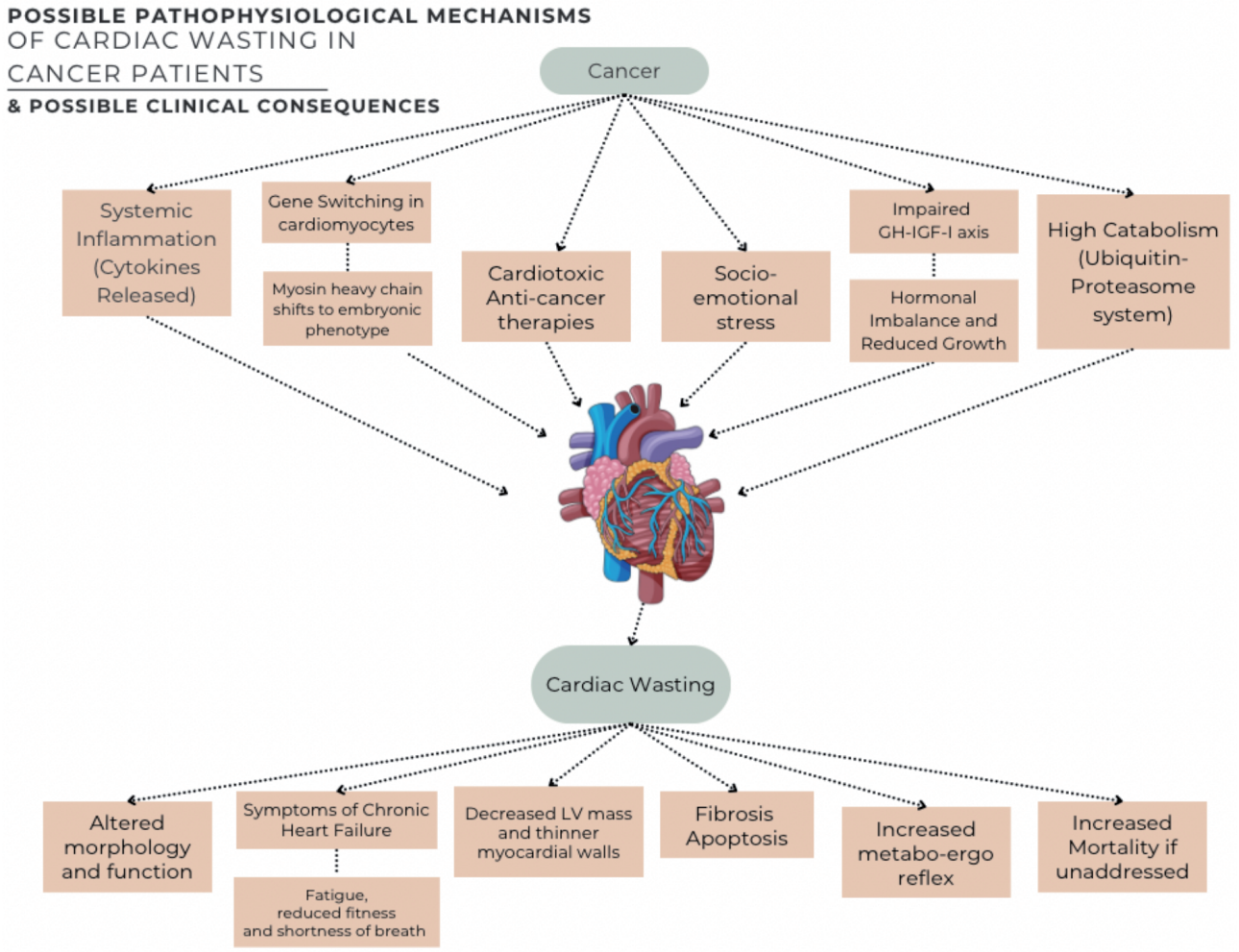

Figure 1. Possible pathophysiological mechanisms of cardiac wasting in cancer patients and possible clinical consequences**.** Several pathophysiological mechanisms in cancer patients, such as widespread Inflammation, myosin heavy chain shift, high catabolism, hormonal dysregulation, GH resistance, metabolism of cardiotoxic anticancer therapies and associated psychosocial stress, can adversely affect the heart, leading to cardiac atrophy. This condition is characterized by alterations in cardiac structure and morphology, particularly in the left ventricle. These changes often present with symptoms resembling those of chronic heart failure, as well as an increased metabo-ergo reflex. If left unaddressed, this cardiac damage might contribute to elevated mortality rates in cancer patients. GH, growth hormone; IGF, insulin-like growth factor-I; I, IGF-binding protein 3.

advanced cancer patients, and non-cancer-related mortality accounts for 20-30% of deaths in this cohort.[3,4,6] Additionally, distinguishing between cancer-induced cardiac wasting and chronic heart failure is clinically challenging, as both conditions share symptoms such as fatigue, exercise intolerance, dyspnea, and impaired quality of life. Furthermore, the risk of sudden cardiac death is elevated in these patients.[7,11,18,46-49]

Morphologically, advanced cancer patients show significant alterations in cardiac structure and function, including a reduction in left ventricular mass, decreased global longitudinal strain (GLS), and diminished posterior wall thickness, as observed in murine models (C26 and CD2F1) and human studies.[11,17,21,50] Interestingly, while left ventricular ejection fraction (LVEF) declines in some cases, it may remain preserved and hence, cannot be classified as a reliable marker of cardiac dysfunction in this context.[6]

Multiple studies, including those by Aimo *et al.* and Anker *et al*., have explained the «muscle hypothesis» in the context of cardiac cachexia.[51,52] This hypothesis states that left ventricular dysfunction in cachectic patients leads to an enhanced catabolic state, ultimately exacerbating skeletal muscle wasting.[53] This process creates a positive feedback loop, wherein the accelerated muscle degradation causes hyperactivation of the metabo-ergo reflex - a synergistic response involving the metabo-reflex and mechanoreflex of skeletal muscles.[52] This heightened reflex activity increases ventilatory demand in the face of reduced muscle mass, resulting in excessive ventilation. This hyperventilation contributes to the induction of dyspnea and exercise intolerance.[54] Increased metabo-ergo reflex also leads to excessive stimulation of the sympathetic nervous, leading to vasoconstriction, elevated peripheral resistance, and increased afterload.[53-58] These circulatory effects further impair cardiac function, perpetuating the cycle of worsening cardiac wasting.[7] Despite its significance, this aspect of cardiac cachexia remains insufficiently studied in the context of advanced cancer patients and warrants further investigation to establish a direct link.

Current evidence on cardiac wasting in advanced cancer patients

Preclinical evidence

Preclinical evidence on cardiac wasting in cancer patients dates back to 1978, when Ludholm *et al.* first compared metabolic alterations in tumor-bearing mice (C-57) with sarcoma (MCG-101) to 52 cancer patients.[59] The study revealed higher activity of lysosomal enzymes in both skeletal and cardiac tissues of the mice, accompanied by a decrease in total protein content and a reduction in cardiac muscle mass.[59] In 1987, Sjostrom *et al*. examined the ultrastructure of hearts extracted from mice 11 days post-tumor implantation, identifying signs of cardiac atrophy.[14] They reported a 33% reduction in the cross-sectional area of cardiomyocytes, alongside lower levels of myofibrillar, soluble, and collagen proteins.[14]

Drott *et al.* in 1989 further confirmed that all three types of cardiac proteins (myofibrillar, soluble, and collagen) were reduced in both mice and rats.[60] Their findings demonstrated a marked decrease in heart weight and total protein content, mediated by both diminished synthesis and elevated degradation.[60] In 2001, Welsh *et al*. observed that despite significant structural changes in the hearts of inbred male Lewis rats, including a 41% decrease in cardiomyocyte volume and a 26% reduction in cross-sectional area, the contractile function was preserved, with the LVEF remaining intact.[15] Artaza *et al*. expanded on this concept, identifying myostatin, an endogenous negative regulator of heart and left ventricular size, as a crucial factor.[16] Overexpression of myostatin in transgenic mice led to an 11% reduction in heart weight and a 21% decrease in left ventricular mass, while LVEF remained normal.[16] These findings highlight the heart's compensatory mechanisms to protect its function despite structural atrophy.

Tian *et al.* in 2010 introduced an *in vivo* study using CD2F1 mice, which were divided into tumor, no-tumor, and pair-fed groups.[47] The tumor group was inoculated with colon-26 adenocarcinoma, leading to cachexia characterized by a 23% reduction in body weight, significant skeletal muscle loss, and cardiac abnormalities.[47] Histological analysis revealed fibrosis, disrupted sarcomere arrangement, and impaired mitochondrial integrity. Biochemically, contractile protein composition was altered, with a 38% decline in troponin I gene expression, a 33% reduction in MyHC-alpha mRNA, and a 93-fold increase in MyHC-beta expression.[47] Inflammatory cytokines were elevated, with significant increases in IL-6 and IL-6 receptors (5.7-fold and 2.3-fold, respectively), as well as a 1.9-fold increase in F4/80, a marker of macrophage invasion in the heart.[47]

In the same year, Zhou *et al*. explained the critical role of a unique signalling pathway in the pathogenesis of cancer cachexia, mediated by ActRIIB, which is a high affinity activin type 2 receptor, responding to a subset of TGF-beta family ligands including myostatin, activin, GDF11, *etc*.[26,61,62] Zhou *et al*. demonstrated the ligand-neutralising effects of ActRIIB antagonist, sActRIIB, first on C2C12 myoblasts, inhibiting both myostatin- and activin-mediated signal transduction, and then on adult C57Bl/6 mice, which resulted in dose-dependent elevations of body weight and lean mass.[26] Additionally, sAcRIIB administration in C26 mice was found to cause the complete reversal of cancer-induced cardiac atrophy, which gives us evidence on the role of ActRIIB in the development of cardiac wasting in cancer patients.[26] Interestingly, this ActRIIB blockade in mouse models nullified the wasting effects of ubiquitin ligases in muscles, but no difference was observed in the expression of atrophy-specific ubiquitin ligases in atrophic heart, therefore the pathophysiological mechanisms behind this reversal require further investigations.[26]

In 2011, Cosper *et al*. assessed cardiac atrophy in colon-26 adenocarcinoma-bearing CD2F1 mice in a sexually dimorphic manner, challenging previous assumptions regarding the role of apoptosis in cardiac wasting.[63] They found that autophagy, rather than apoptosis, was responsible for cardiac atrophy, as evidenced by no upregulation of the ubiquitin-proteasome sys-

tem.[63] Consequently, a direct link was established between cardiac atrophy and a decrease in cardiomyocyte size and not cardiac cell death, owing to the 31% smaller cross-sectional area in males and 16% smaller in females.[63] While the decrease of selective proteins in the later stages of cardiac atrophy is a controversial topic in research, they observed a parallel decrease in all sarcomeric proteins, with 22% loss contributed by MyHC.[63] Additionally, both male and female hearts exhibited significant increases in fibrosis, 50% and 65% respectively.[63] Functionally, male atrophic hearts in males had marked reductions in aortic pressure and aortic velocity, with the decreases being 30% and 16% respectively, while female hearts showed no decline in these functional parameters.[63] This was experimented upon to be due to estrogen signalling required to sustain cardiac muscle mass, as demonstrated by the appearance of male-like cardiac mass loss with the administration of an estrogen receptor antagonist, Fulvestrant, in this study.[63] In both sexes, ejection fraction or fractional shortening was found to be preserved.[63]

In the same year (2011), Tian *et al*. observed molecular-level changes in CD2F1 mice with C26 tumors, noting increased fibrosis and a shift in MyHC from adult to fetal isoforms, as well as decreased GLUT4 expression.[21] Related to increased proteolysis in cachexia, there was 43% loss of MyHC, 58% reduction in troponin I and marked elevation in protein ubiquitination, owing to the hyperactive UPS.[21] There was significantly reduced fractional shortening, 28% decrease in interventricular septum, 30% decrease in posterior wall thickness and 21% loss of heart mass.[21] Inflammatory cytokines were highly elevated, with a 100-fold increment in IL-6 and there was notable activation of p44/42 MAPK in the myocardium.[21] Also in 2011, Mühlfeld *et al.* studied the Lewis lung carcinoma model over 21 days, reporting a 12-15% decrease in total body weight and a 50% reduction in left ventricular axon length, which they attributed to hypoinnervation of the myocardium.[64] This study revealed differences in morphology and cardiac function compared to Tian *et al*. model, although cardiac function was relatively preserved in the tumor group in this study.[64]

Together, these preclinical studies provide critical insights into the molecular and structural mechanisms underlying cardiac wasting in cancer, highlighting potential therapeutic targets and pathways for intervention in future clinical research. The studies are summarized in Table 1.

Clinical evidence

In 2014, Springer *et al*. conducted a comparative study between the rat AH-130 hepatoma model and human patients who succumbed to cancer cachexia, highlighting several notable similarities in cardiac atrophy.[13] These included fibrosis, a 58% reduction in left ventricular (LV) mass, a 25.6% decrease in heart weight, a 12.1% reduction in LV wall thickness, and a 35% decline in overall lean mass.[13] Furthermore, the study reported significant elevations in plasma levels of aldosterone (2.1-fold increase), renin (2.9-fold increase), and brain natriuretic peptide (3.0-fold increase) in these cachectic patients.[13] In the same year, Cramer *et al.* conducted the first prospective study examining the relationship between cardiovascular parameters and impaired exercise capacity in colorectal cancer (CRC) patients.[46] Their findings demonstrated a modest reduction in left ventricular ejection fraction (LVEF) and a significant decline in peak oxygen consumption and breathing efficiency in both therapy-naive and chemotherapy-treated CRC patients.[46] Similar cardiovascular changes were also observed in patients with chronic heart failure (CHF), thus establishing a symptomatic link between these two chronic conditions.[46]

In 2017, Barkhudaryan *et al.* performed a retrospective analysis based on autopsy reports of 177 cancer patients, assessing cardiac function through heart weight, relative heart weight, LV wall thickness (LVWT), and right ventricular wall thickness (RVWT).[6]) Their findings revealed a 19% reduction in cardiac mass in cancer patients with cachexia compared to those without cachexia.[65] This study provides compelling evidence supporting the association between advanced cancer and cardiac wasting, as evidenced by the observed decrease in heart weight in cadavers.[65] In 2018, Potter *et al*. emphasized the need for replacing LVEF with Global Longitudinal Strain (GLS) for more accurate assessment of left ventricular function.[17] GLS was found to be more sensitive, detecting reductions in cases of preserved LVEF due to compensatory mechanisms in cardiac dysfunction. One relevant example was cardiotoxicity induced by anticancer therapies, where GLS showed a 15% reduction.[17,66]

Also in 2018, Jordan *et al*. identified early declines in LV mass as a critical biomarker of cardiac wasting in cancer patients exhibiting preserved LVEF.[67] Their study provided insights into the pathophysiology of cardiac atrophy associated with anthracycline-induced cardiotoxicity, revealing a 5% loss in LV mass, increased LV afterload, and mild heart failure symptoms within six months of initiating treatment.[67] In 2019, Kazemi-Bajestani *et al*. conducted a 112-day investigation into LV mass and cardiac function in 50 patients with non-small cell lung carcinoma undergoing carboplatin-based palliative chemotherapy.[5]) They compared various cardiac parameters pre- and post-treatment, revealing a significant anatomical change with an 8.9% loss in LV mass.[50] This was accompanied by a notable functional change, including an 8.1% decline in GLS.[50] These findings highlight the impact of chemotherapeutic agents on left ventricular structure and systolic function. However, a limitation of this study was the partial observation of the total LV mass loss over 3.7 months, given the median survival of these patients was typically 15 months.[50]

In 2023, Lena *et al*. prospectively examined 300 cancer patients between 2017 and 2020, classifying them into cachectic and non-cachectic groups.[11] Their study revealed a substantially reduced LV mass in advanced stage cancer patients - 25% and 8% lower LV mass in cachectic and non-cachectic patients, respectively, (average 13%) when compared to healthy controls of similar age and sex - along with decreased stroke volume and thinning of the LV walls.[11] Follow-up evaluations indicated elevated levels of circulating IL-6 and C-reactive protein, while levels of IL-1 and TNF remained unchanged.[11] This reduction in LV mass and associated cardiac wasting were linked to impaired physical performance, including decreased handgrip strength,

6-minute walking distance, and stair-climbing power.[11] Therapy-naive, non-cardiotoxic therapy, or cardiotoxic therapy status had no influence on LV mass. The patient population consisted of hospitalized patients (at baseline assessment), mostly with advanced cancer, which could have contributed to cardiac atrophy due to immobility or prolonged bed rest – which is often seen in patients with very advanced stages of cancer disease.[11] Perhonen *et al*. (2001) and de Groot *et al*. (2006), observed LV mass reductions of 15% and 25%, respectively, in individuals undergoing prolonged bed rest or with spinal cord injury.[68,69] This raises questions regarding whether the aetiology of cardiac atrophy in advanced cancer patients is primarily cancer-related or maybe additionally also a consequence of physical inactivity. Table 2 summarizes findings from key clinical studies.

Future implications in clinical practice and research advancements

Cardiac events are recognized as leading causes of death in patients of advanced cancer, following multi-organ failure and

Table 1. Preclinical evidence.

Author (year)	Models	Outcomes
Lundholm *et al.*[59] (1978)	C57BL/J mice 52 cancer patients	↑ Activity of lysosomal enzymes ↓ Cardiac muscle mass ↓ Total protein content
Sjostrom *et al.*[14] (1987)	C57BL/J mice	Signs of cardiac atrophy 33% ↓ Cardiomyocyte cross-sectional area ↓ Tyofibrillar, soluble, and collagen proteins
Drott *et al.*[60] (1989)	Female C57B1/J mice and male Sprague-Dawley rats	↓ Myofibrillar, soluble, and collagen proteins ↓ Heart weight ↓ Total protein content
Welsh *et al*.[15] (2001)	Inbred male Lewis mice	41% ↓ cardiomyocyte volume 26% ↓ cardiomyocyte cross-sectional area LVEF preserved
Artaza *et al*.[16] (2007)	C57BL/J mice	Overexpression of myostatin 11% ↓ heart weight 21% ↓ left ventricular mass LVEF preserved
Tian *et al*.[47] (2010)	CD2F1 male mice with colon-26 adenocarcinoma	Signs of cachexia 23% ↓ body weight 38% ↓ troponin I 93-fold ↑ MyHC-beta expression Cardiac cells; fibrosis, disrupted sarcomeres, impaired mitochondrial integrity 5.7-fold ↑ in IL-6
Zhou *et al*.[26] (2010)	C57BI/6 mice	Ligand-neutralising effects of ActRIIB antagonist, sActRIIB ↑ Body weight and lean mass Complete reversal of cardiac atrophy
Cosper *et al*.[63] (2011)	CD2F1 male and female mice with colon-26 adenocarcinoma	↓ Cardiomyocyte cross-sectional area (31% in males, 16% in females) ↑ fibrosis 30% ↓ aortic pressure 16% ↓ aortic velocity LVEF preserved
Tian *et al*.[21] (2011)	CD2F1 male mice with colon-26 adenocarcinoma	↑ Fibrosis and a shift in MyHC 43% loss of MyHC, 58% reduction in troponin I ↑ Protein ubiquitination 30% ↓ posterior wall thickness 21% ↓ heart mass 100-fold ↑ in IL-6
Mühlfeld *et al*.[64] (2011)	Mice with Lewis lung carcinoma	12-15% ↓ total body weight 50% ↓ left ventricular axon length Cardiac function relatively preserved

LVEF, left ventricular ejection fraction; MyHC, myosin heavy chain; IL-6, interleukin-6; ActRIIB, activin receptor type II B; sActRIIB, soluble activin receptor type II B.

sepsis.[1] Hence, there is a need for more attention and further research on cardiac wasting in this population. The phenomenon of cardiac wasting / atrophy, characterized by alterations in left ventricular morphology and impaired histological structure, has been observed in numerous preclinical and clinical trials involving patients with cancer at various stages of the disease, particularly in advanced stages.[11,50] This necessitates the integration of routine cardiac assessment in both clinical practice and research involving cancer patients. Cardiac wasting has been identified as a major contributor to mortality, possibly responsible for up to 20-30% of cancer-related deaths. Additionally, increased resting hearts rates and ventricular cardiac arrythmias have been observed in cancer patients, despite LVEF being normal.[3,70-73] Given this, it is essential to broaden the focus from solely cancer-related symptoms to encompass the management of cardiovascular abnormalities, particularly in palliative care settings.

Traditional measures such as left ventricular ejection fraction (LVEF) have been shown to be unreliable as indicators of cardiac dysfunction due to the compensatory mechanisms that maintain LVEF despite significant reductions in cardiomyocyte area and protein content.[15,16] A more accurate and sensitive parameter might be Global Longitudinal Strain (GLS), which has demonstrated superior ability in detecting left ventricular dysfunction.[17] GLS should therefore be assessed along with LVEF in both clinical practice and future clinical trials for more precise cardiac monitoring.

Inadequate stratification of cancer patients, as exemplified by Lena *et al*., complicates efforts to accurately define the pathophysiology and prognosis of cardiac dysfunction.[11] Proper patient classification according to therapy status (i.e., therapy-naive, on non-cardiotoxic therapies, or on known cardiotoxic therapies) is essential in distinguishing between cancer-induced cardiac cachexia and therapy-induced cardiac dysfunction. Moreover, hospital-based and immobile patient populations in clinical trials pose an additional challenge, as physical inactivity itself can contribute to cardiac atrophy.[68,69] Therefore, future trials must assess the mobility status of cancer patients to better understand the multifactorial nature of cardiac wasting. Additionally, we found only a few studies comparing cancer patients to that of heart failure, however, further investigation is required to establish a definitive etiological link to explain the symptomatic similarities. This etiological link requires researchers to modify their inclusion criteria and ascertain whether patients had pre-existing cardiovascular disorders or whether cancer was directly involved in their development.

To enable early detection, accurate prognosis, and precise evaluation of therapeutic responses, the adoption of advanced technologies is essential. Imaging techniques such as echocardiography, cardiac magnetic resonance imaging (MRI), and positron emission tomography (PET) offer superior sensitivity in detecting cardiac abnormalities when compared to traditional methods. Furthermore, specific biomarkers such as troponin I, brain natriuretic peptide (BNP), and Myosin Heavy Chain (MyHC) isoform shifts hold prognostic value and can aid in predicting adverse cardiac events in cancer patients. Regular monitoring through these advanced methodologies should be incorporated into follow-up protocols for advanced cancer patients.

Table 2. Clinical evidence.

Author (year)	Number of participants	Outcomes
Springer *et al*.[13] (2014)	2 sets First set = 37 Second set = 76	58% ↓ LV mass 25.6% ↓ heart weight 12.1% ↓ LV wall thickness 35% ↓ overall lean mass ↑ Aldosterone, renin, BNP
Cramer *et al*.[46] (2014)	152	Mild ↓ LVEF ↓ Peak oxygen consumption ↓ Breathing efficiency
Barkhudaryan *et al*.[65] (2017)	177	19% ↓ cardiac mass
Potter *et al*.[17] (2018)	N/A	GLS is a more sensitive marker of cardiac atrophy than LVEF
Jordan *et al*.[67] (2018)	100	Anthracycline-induced cardiotoxicity 5% ↓ LV mass ↑ LV afterload Mild heart failure symptoms
Kazemi-Bajestani *et al*.[50] (2019)	50	8.9% ↓ LV mass 8.1% ↓ GLS
Lena *et al*.[11] (2023)	300	↓ LV mass ↓ Stroke volume ↓ LV wall thickness ↑ IL-6 and C-reactive protein Impaired physical performance

LV, left ventricle; BNP, brain natriuretic peptide; LVEF, left ventricular ejection fraction; GLS, global longitudinal strain; IL-6, interleukin-6.

While significant progress has been made in understanding the mechanisms behind cardiac atrophy in cancer patients, including systematic inflammation, increased catabolism, impaired GH-IGF-I axis, MyHC switching, oxidative stress, psychosocial stress and particularly, on the effect of cardiotoxic anti-cancer therapies, a definitive confirmation of the underlying pathophysiology is still lacking. Future research should focus on identifying specific gene expression patterns associated with cardiac wasting in cancer patients. Studies like Tian *et al*. have highlighted the importance of determining the time course of cardiac dysfunction before the clinical manifestation of symptoms.[47] Early detection and timely intervention may prevent or reverse cardiac damage, underscoring the need for further investigation into the underlying mechanisms.

There remains a notable gap on the efficacy of pharmacologic therapies in the management of cardiac abnormalities in human cancer patients. In preclinical models, ACE inhibitors (ACEi), angiotensin receptor blockers (ARB), mineralocorticoid receptor antagonists (MRA) and beta blockers have shown different effects. Imidapril, an ACEi, did not show any improvement in survival, while other ACEi were successful in reducing the progression of cardiac atrophy. The same was observed for the rest of classes of drugs, but all data originated from preclinical studies.[6,13,19,74-76] Therefore, this absence of human-derived data warrants future clinical trials to be specifically focused on human cancer patients to ascertain which medications can directly address cardiac wasting in this population.

Moreover, therapies aimed at counteracting the cardiotoxic effects of certain anti-cancer agents, such as dexrazoxane for anthracycline-induced toxicity, require further exploration to mitigate therapy-mediated cardiac damage.[77] In clinical trials assessing the safety and efficacy of various interventions, it is essential to utilize multiple primary endpoints to provide a comprehensive evaluation of diverse clinical outcomes.[78] These endpoints should be strategically focused on improving survival rates, reducing length of hospital stays, and safely enhancing functional capacity.[79] This multi-dimensional approach ensures a thorough assessment of the intervention's impact across key aspects of patient health and well-being. Furthermore, the integration of non-pharmacologic interventions such as exercise, resistance training, and nutritional support has also shown promise in improving cardiac outcomes, but more clinical studies are needed to substantiate these findings.[6]

Given the extensive overlap between cancer and cardiovascular disease, the expansion of the field of cardio-oncology is essential. A more multi-disciplinary approach would facilitate the integration of cardiac and cancer-specific biomarkers into routine clinical practice, ensuring a comprehensive approach to managing both cancer and cardiovascular health. Early intervention, facilitated by the incorporation of cardiac monitoring into oncological care, could significantly improve the quality of life and lifespan of cancer patients, especially when cardiac dysfunction is identified and treated early in the disease trajectory.[80-82] These future implications are illustrated in Figure 2.

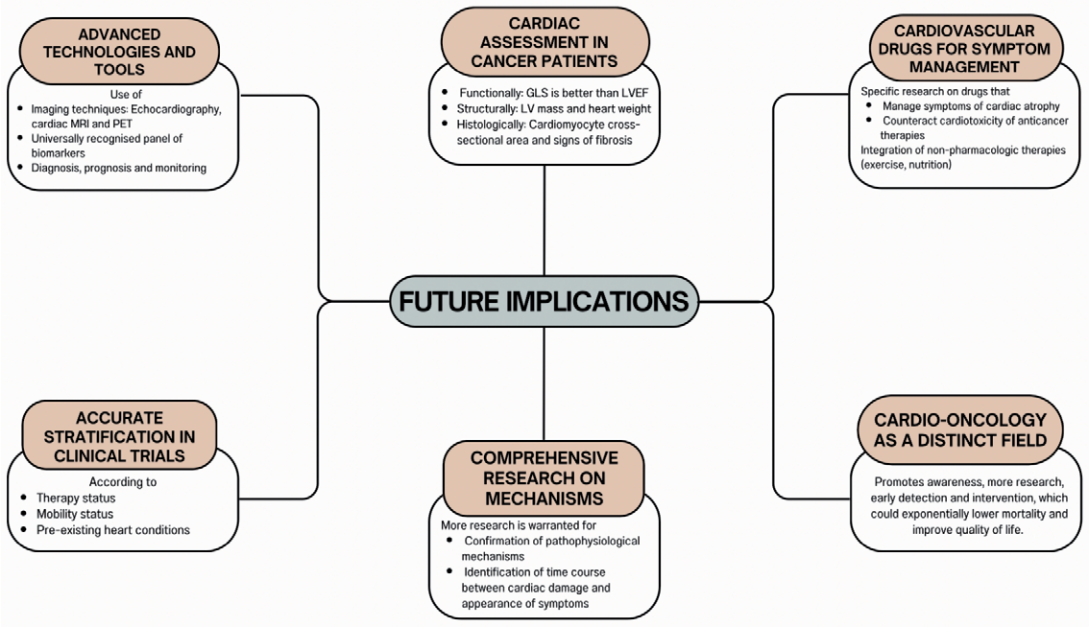

Figure 2. Future implications related to cardiac wasting in cancer patients. Cardiac assessment should be routinely integrated into the checkups and follow-up care of cancer patients. The use of advanced diagnostic tools, coupled with a comprehensive panel of biomarkers, is essential for accurate diagnosis, prognosis, therapeutic interventions, and ongoing monitoring. Further research is needed to evaluate the efficacy and safety of cardiovascular drugs and to elucidate the precise mechanisms underlying the development of cardiac wasting. Clinical trials must ensure appropriate stratification of patient groups to yield reliable and meaningful outcomes. Additionally, the promotion of a multidisciplinary approach is crucial to advancing the field of cardio-oncology. MRI, magnetic resonance imaging; PET, positron emission tomography; GLS, global longitudinal strain; LVEF, left ventricular ejection fraction; LV, left ventricle.

Conclusions

Cardiac wasting is a prevalent and often underrecognized complication in advanced stage cancer patients. Its multifactorial pathogenesis and severe clinical consequences necessitate dedicated research to develop effective diagnostic and therapeutic strategies. Addressing this condition has the potential to substantially improve patient outcomes and survival rates.

Conclict of interest

MSK reports receiving fees from Bayer and Novartis. All other authors report no conflict of interest.

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